Scrotal Pathologies

Introduction

This lesson is titled "Scrotal Pathologies," but it doesn't actually cover any disease or disorder of the scrotal sac itself. Within the scrotum are the tunica vaginalis Peritesticular Cavity, epididymis, and testes, as well as connections to the retroperitoneal abdominal cavity—arteries, veins, lymphatics, and nerves. This lesson covers three categories of conditions: those that cause scrotal swelling without pain and are not cancer, those that cause scrotal swelling with pain and are not cancer, and those that are testicular cancer. This categorization is less targeted at helping you with clinical reasoning and more at helping mechanistically. Although this may feel hodge-podgy (it is), we've tried to at least silo these conditions into clinical buckets to help them stick in your memory—painless swelling not cancer, painful swelling not cancer, and swelling that is cancer.

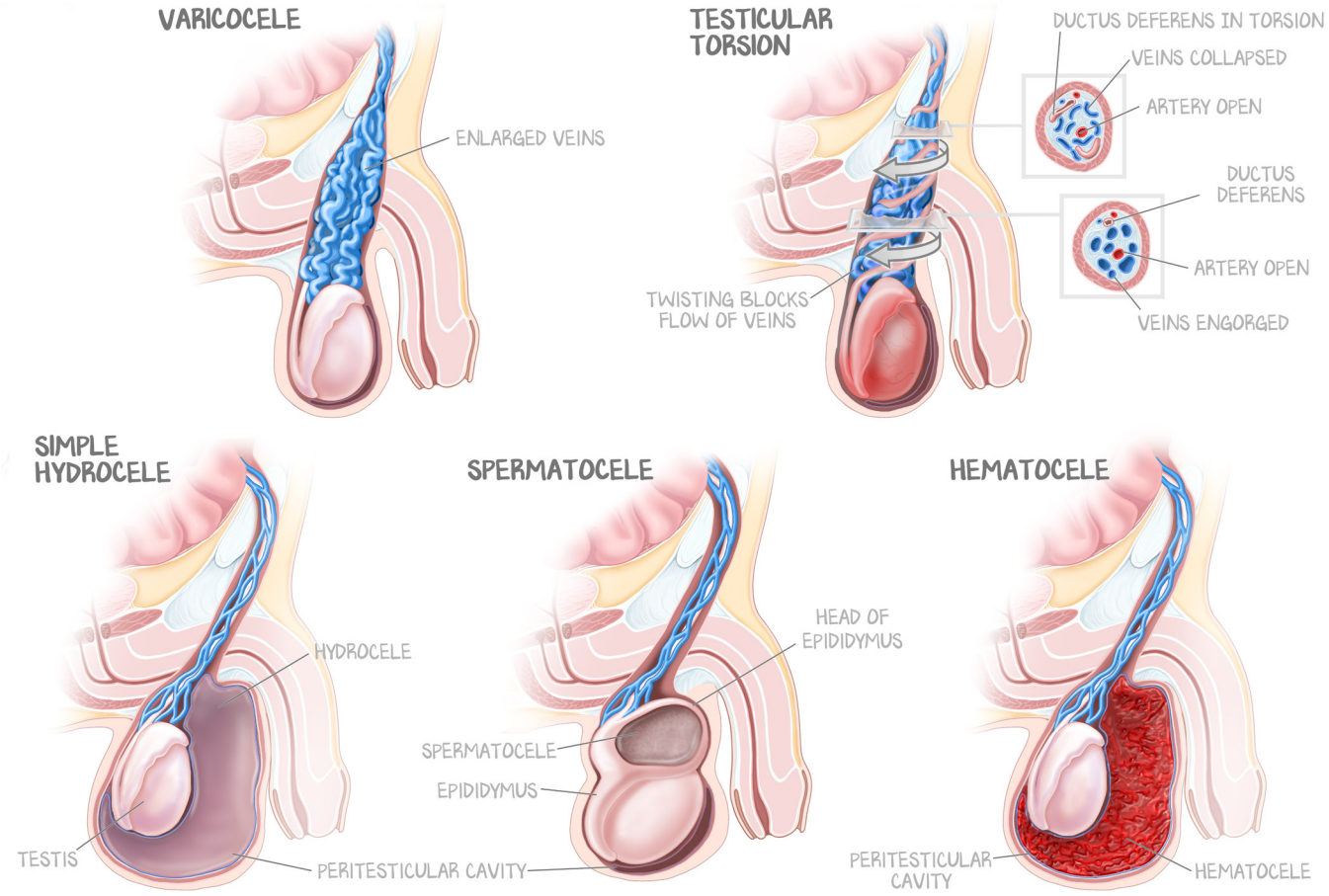

Figure 3.1: Common Scrotal Pathologies Illustrated
A preview of the pathologic states of the scrotal structures in this lesson.

Painless Scrotal Swelling Not Cancer

The conditions discussed in this section are generally caused by an accumulation of fluid in something other than the testis itself—fluid in the Peritesticular Cavity (hydrocele), fluid in the epididymis (epididymal cyst, spermatocele), or blood backed up in the pampiniform plexus (varicocele). Each causes low-acuity, low-severity, painless swelling of the scrotum. Low acuity and low severity mean that the diagnosis can be delayed in favor of limiting unnecessary tests, and treatment may not even be required at all. This is, of course, assuming that it isn't cancer. As we discuss below, the diagnosis of testicular cancer involves orchiectomy—removal of the testis—and NOT a simple biopsy. If you are able to diagnose one of the benign conditions we discuss, then surgical removal of a testis to exclude cancer won't be considered. That is why this lesson is organized the way it is—if there is swelling of the region around the testis, always consider cancer, but don't always do an orchiectomy! Remember: cancer will always be an initial consideration, but the presence of one of these benign diagnoses means you probably won't proceed to evaluating for cancer.

Two key physical exam features make scrotal swelling far less likely to be cancer: transillumination and exacerbation with Valsalva maneuver. Although no single test guarantees that a lesion isn't malignant, at this stage in your training, we want you to learn that "*if there is transillumination or exacerbation with Valsalva, there is no cancer.*" **Transillumination** (shining a light through the swollen skin to see whether it illuminates the other side) facilitates the diagnosis of hydrocele and spermatocele. Temporary **exacerbation by Valsalva maneuver** (enlargement of the mass with increased abdominal pressure) and its cousin, temporary improvement with lying flat, are used to diagnose varicocele and bowel herniation into the scrotal sac. Testicular cancer does not show transillumination and does not respond to Valsalva.

Hydrocele is excess fluid in the Peritesticular Cavity, which is a remnant of the processus vaginalis (an evagination of and continuous with the peritoneal cavity) that accompanied the descending testis (one processus vaginalis for each testis, one Peritesticular Cavity per testis) during embryogenesis. The Peritesticular Cavity (a Body Cavity; a fluid-filled sac lined with mesothelium) should have no connection to the peritoneal cavity (a Body Cavity; a fluid-filled sac lined with mesothelium). We discussed persistent tunica vaginalis in Gastrointestinal, where indirect hernias were caused by this defect. It gave us the neonatal hernia—although more apparent in males, it can also happen in females. A patent connection between the Peritesticular Cavity and the peritoneal cavity (i.e., the scrotal Body Cavity and the abdominal Body Cavity) means baby is going to present with a hernia early in life. Therefore, **adult hydrocele** must have nothing to do with the processus vaginalis. Body Cavities are fluid-filled sacs lined with mesothelium. That fluid is serous, straw-colored, and mostly transparent. Recall from the Cardiac module that excess serous fluid in a compartment is *fluid where fluid shouldn't be*. The mesothelium makes the fluid as padding for the testes and to orient the epididymis to be posterior and superior to the testes. The fluid produced by the mesothelium must be drained. Body Cavities are drained by lymphatics. Because the Peritesticular Cavity is mesothelium, it is theoretically possible to develop mesothelioma there, and it's theoretically possible that excess fluid may be made. In practice, that just isn't the case. Instead, adult hydroceles in developed countries are almost always **iatrogenic**, a complication of **hernia repair**. Unintentional surgical damage, either intraoperatively or in securing the mesh of the "hernia hideout," can compromise the drainage of the Peritesticular Cavity, creating a hydrocele. Hydroceles don't need to be treated if they remain small and asymptomatic. However, they may become bothersome, cause cosmetic defects, or, if they get large, compromise urination and fertility. The swelling will **transilluminate**, will be **generalized** (see spermatocele), and will **not change with position or Valsalva maneuver**. Confirmation is made with **ultrasound**. Never drain a hydrocele—it does not fix the underlying pathology, and the fluid will just reaccumulate. Surgical correction is needed. In that case, the sac is opened (marsupialized), allowing the fluid to be drained by the testicular vessels—veins and lymphatics. Adult hydrocele in developing countries is usually caused by infection—*Wuchereria bancrofti* filariasis or *Chlamydia trachomatis* L serotypes.

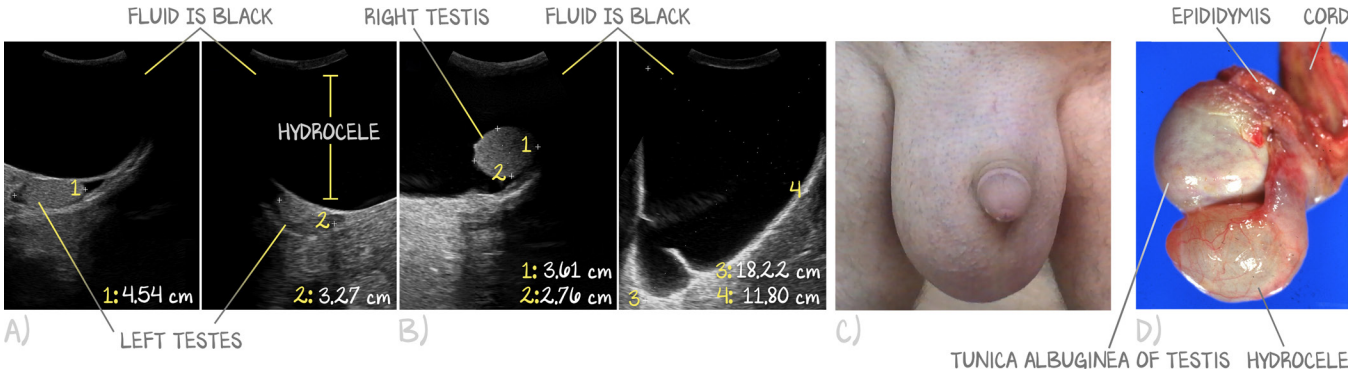

Figure 3.2: Hydrocele
(a) A left testicular ultrasound demonstrates a massive hydrocele. On ultrasound, fluid is black. At the top of both images, the curved grey line represents skin, and the curved bright white line above the testis is the edge of the Peritesticular Cavity. The left testis and its Peritesticular Cavity are being compressed by the hydrocele, though the testis is of normal size (4.54 cm × 3.27 cm). (b) A right testicular ultrasound demonstrates the hydrocele compressing the right testis against the wall of the scrotum. The testis is normal in size (3.61 cm × 2.76 cm). The accompanying image in (b) demonstrates the size of the hydrocele at its largest (18.22 cm × 11.80 cm), and no testis is visible. (c) A photograph taken from the same patient as the ultrasound, demonstrating a uniform swelling of the right testis (left side of image). The penile shaft is not visible, and only the glans penis can be seen. (d) This pathologic sample was taken from another patient (orchiectomy is not indicated for hydrocele), who had an incidental, and small (the hydrocele is about the size of the testis), hydrocele.

Spermatocele is excess fluid in the epididymis, typically in its head. Spermatocele, like hydrocele, is more a cosmetic annoyance than a serious pathology. Spermatocele rarely occludes the lumen of the epididymal duct distal to all efferent tubules, so fertility is usually not compromised despite the continuously growing swelling caused by fluid. If large enough, a spermatocele can impair sexual function and eventually cause infertility. Almost identical to hydrocele, this painless scrotal swelling **transilluminates**, does **not change with position or Valsalva maneuver**, is confirmed with an **ultrasound**, and is **surgically treated**. Where this differs from hydrocele is its location. The head of the epididymis is located posterior and superior to the testis. Thus, the swelling of a spermatocele will be located posterior and superior to the testes. This means the physical exam is not uniform (it is focal rather than generalized) as it was in hydrocele. Spermatocele is caused by the blockage of flow within or into the epididymis. Because there are many tributaries into the epididymal duct (multiple efferent ducts from the rete testis), and because spermatocele most often occurs in the head of the epididymis, the obstruction is often incomplete. And because the epididymal duct is a highly convoluted duct, it has the extra capacity to swell and accommodate excess fluid. The dilated portion of the epididymis will lose its convoluted appearance and become stretched out, but because there is so much excess tubing, fertility will remain unimpaired despite the swelling (unless really big, as stated earlier). If it gets too big or fertility is compromised, surgery is performed to remove the affected segment.

Varicocele is excess blood in the pampiniform plexus. The testicular arteries bring blood into the scrotum through the spermatic cord, perfusing the testis, epididymis, and Peritesticular Cavity. In order to cool that blood, there isn't just a testicular vein, but rather an elaborate network of veins that surrounds the testicular artery. Several tributaries out of the pampiniform plexus converge to form the testicular vein. They don't connect except at the convergence of vessels in the pelvis, outside the inguinal canal. Arteries are already high-pressure vessels and, relative to the heart, blood flow down the arteries into the scrotum is further facilitated by gravity. So much so that the arterioles dampen the perfusion pressure down to what their capillaries want it to be, and the hydrostatic pressure is exhausted within the capillary. Like every other capillary bed, the veins are low-pressure and usually have to contend with gravity to move blood up to the inferior vena cava (IVC). If part of the pampiniform plexus becomes occluded for any reason, blood is going to have a tough time getting out of the scrotum. Thus, as blood flow in is not compromised but blood flow out is, the affected veins will engorge, giving the scrotum the

appearance of a **bag of worms** (individual engorged vessels becoming visible under the skin). Because this is an issue with the underlying pathology (more on this in a second), and it is worsened by gravity, increasing the pressure the veins contend with will engorge them more, whereas alleviating that pressure will make them less engorged. Thus, the **Valsalva maneuver exacerbates** engorgement, whereas **lying flat alleviates** it. It will **not transilluminate**, and the engorged vessels are found near the external inguinal ring, even more superior to the testis than the epididymis. Ultrasound **with Doppler** confirms the diagnosis (there will be no flow, and the veins will be enlarged cysts). Treatment depends on whether there is a single problematic vessel within the spermatic cord (ablation, ligation, eliminating that diseased vessel's blood flow) or a generalized issue with venous drainage (all vessels affected, meaning a more central problem). Varicocele is more likely to occur on the **left side**. Because the IVC is on the right side of the body, the right adrenal vein, right renal vein, and right testicular vein independently join the IVC. On the left, the left adrenal vein, left renal vein, and left testicular vein converge into one common vein before connecting with the IVC. Because the testicular vein connects at a nearly 90° angle to the renal vein, it is harder for the testicular vein to drain. Most importantly, because renal cell carcinoma spreads hematogenously (and invades the renal vein first), a **sudden onset varicocele in an elderly man** is considered to be renal cell carcinoma until proven otherwise. Ligating or ablating pampiniform vessels won't help if the cause is the cancer (because all veins will be affected), and the cancer is a much bigger problem.

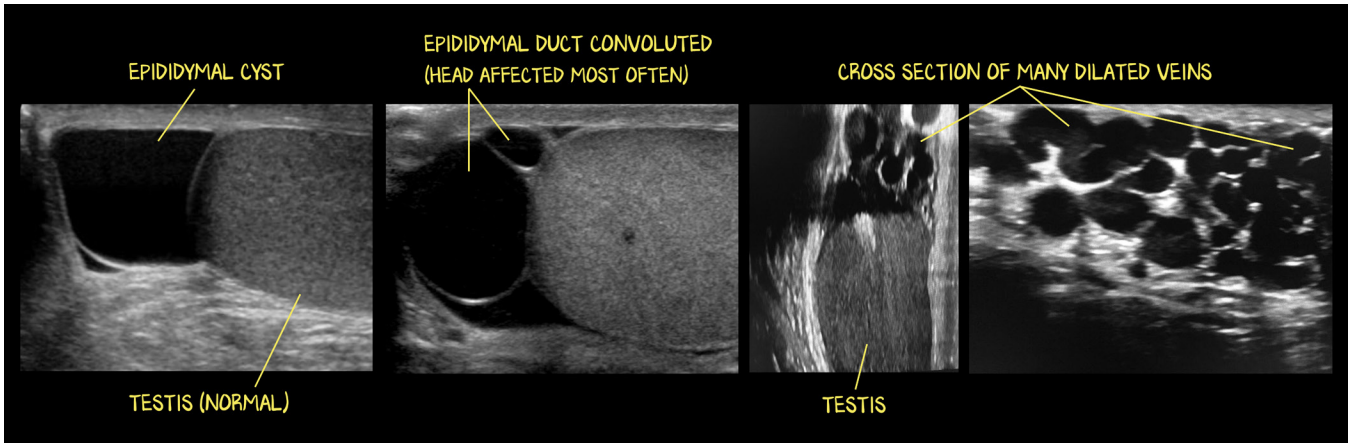

Figure 3.3: Ultrasonographic Spermatocele and Varicocele
The left panel shows an uncomplicated and rather small epididymal cyst/spermatocele. Because fluid shows as black, we know there is only fluid in there. From this perspective, we should see the head of the epididymis, which should have an echogenicity nearly identical to that of the normal testis to the right. In the center panel, it would be appropriate to believe that this was a loculated cyst with compartmentalization. But actually, because the epididymal duct is convoluted, the cyst can appear convoluted on ultrasound as well. The two rightmost panels demonstrate varicocele. Each concentric circle is a vein. All the veins are equally engorged, so there is likely an issue with venous drainage farther down the tract, such as at the insertion of the testicular vein into the left renal vein.

Hernias were covered in Gastroenterology. Male adults are most likely to get a direct hernia (through Hesselbach's triangle, medial to the epigastric vessels, and not through the inner inguinal ring) associated with heavy lifting or other reasons for increased abdominal pressure. It will **not transilluminate**, will be **exacerbated by the Valsalva maneuver**, and will be **reducible** (pushed back in, **better with lying flat**). See Gastrointestinal: Abdominal Wall #2*: Hernias and Small Bowel Obstructions*.

Painful Scrotal Swelling Not Cancer

Pain in the scrotum usually indicates an acute condition. Although it can progress from one of the aforementioned fluid-filled diseases, we want you to clearly separate "inflammation and infarction" (painful) from "obstructed flow" (painless). In cases of **painful scrotal swelling**, especially when there is no evidence or history of trauma, you must always consider testicular torsion. We proceed by discussing the clinical exam maneuvers that can be performed to rule it out—Prehn's sign and the cremasteric reflex—then close this section with torsion.

Prehn's sign has to do with gravity. The testis and epididymis are suspended in the scrotum. Gravity pulls them down. When a structure becomes inflamed (colloquially speaking, and not signifying the histological presence of immune cells), it can hurt for it to be tugged downward. Gravity tugs on the heavier (inflamed) testis or epididymis more than it does on the scrotum. This is effectively the equivalent of pushing on an inflamed joint—the secondary force makes the already tender organ hurt even more. Thus, alleviating the gravitational force (by either having the patient lie flat or lifting the scrotum manually) should lessen the pain. Scrotal pain that is **exacerbated by Valsalva** or **relieved by lying flat** is likely to be inflammatory—epididymitis or orchitis. Testicular torsion is an ischemic event; gravity won't change the fact that a blood vessel is blocked, so testicular torsion shouldn't change with Valsalva or lying flat.

To perform the **cremasteric reflex**, gently stroke the patient's inner thigh, near where the scrotum touches the thigh. What you stroke with is up to you, but you are attempting to trigger a DCMLS-initiated reflex—fine point stroking gently. If the cremasteric reflex is intact, the muscle will contract, and the testis on the ipsilateral side will rise. **A cremasteric reflex** means **torsion is less likely**. Without a cremasteric reflex, you can't be sure whether the reflex is absent, or you just aren't doing it right. Assess on both sides. If you can't elicit the response on the unaffected side, then you cannot interpret the response on the affected side. A positive lift on the side without pain and swelling with a negative lift on the side with pain and swelling tell you this is something serious.

Epididymitis is the inflammation of the epididymal duct. Epididymitis should be considered a **sexually transmitted infection** (STI). In young, sexually active males, the most common causes of epididymitis are **gonorrhea** and **chlamydia** (*Neisseria gonorrhoeae* and *Chlamydia trachomatis* serovars D–K), the culprits of STIs in this age group in general. The urethra is connected to the ejaculatory duct, the lumen of which is the lumen of the ductus deferens, which is also the lumen of the epididymal duct. If the bacteria ascend the urethra (where they cause urethritis), they have access to the ejaculatory duct—the one tube that leads to the epididymis. In elderly men who are not sexually active (we're polarizing the illness scripts to silo them, realizing that a 75-year-old male may still be sexually active and contract STIs), the most common cause of epididymitis is ***E. coli***. If the bacteria ascend into the bladder, they cause a urinary tract infection. If they ascend into the ejaculatory duct, they can eventually arrive in the epididymis. The patient will have a **positive Prehn's sign** (pain is alleviated) and **positive cremasteric reflex** (lifts on the affected side). The epididymis (but not the testis) will be inflamed and tender to palpation. There should be pain on the posterior and superior aspect of the testis—where the head of the epididymis is. Urinalysis with urine culture and PCR for GC/Chlam is enough to make the diagnosis, and antibiotics to treat. Noninfectious causes also occur, and simple over-the-counter analgesics (NSAIDs or acetaminophen) will work. Ultrasound can be performed to rule out torsion, but is often unnecessary.

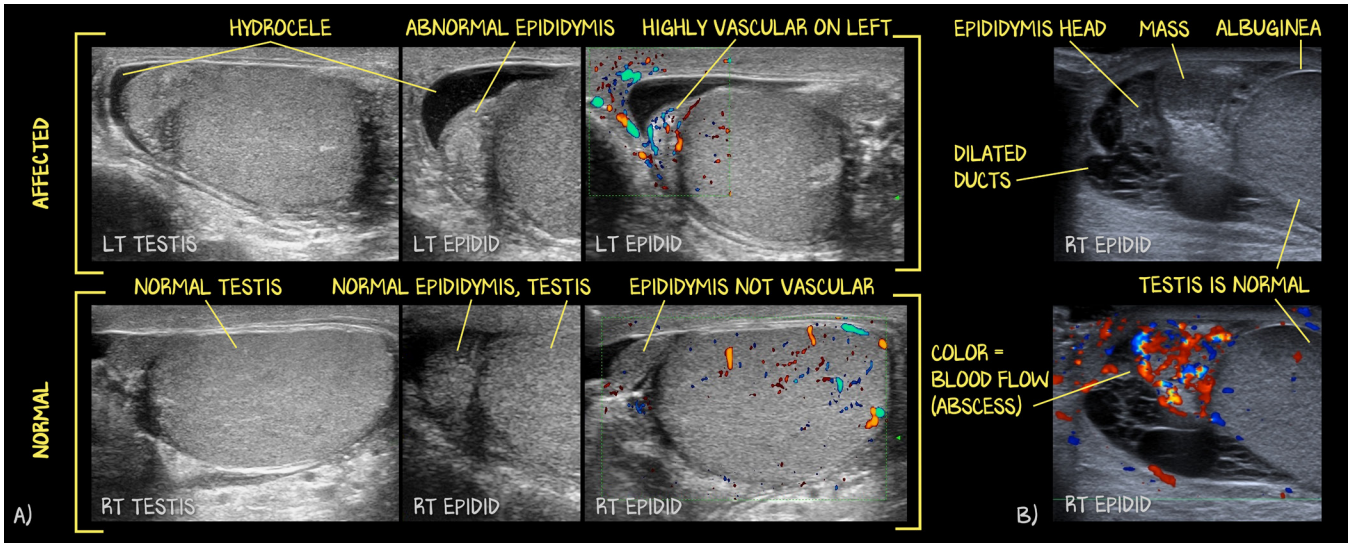

Figure 3.4: Sonographic Epididymal Reactions
(a) Multiple ultrasound recordings compare an affected epididymis (left testis, top row of image) with its unaffected counterpart (right testis, bottom row of image). The first column demonstrates a longitudinal section, showing that the testis is normal in both, but there is a reactive hydrocele on the affected side. In the middle column, the hydrocele is better visualized; there are no alarming changes, but there is obviously different echogenicity in the affected epididymis compared to the unaffected side. The final column is Doppler ultrasound demonstrating vastly increased blood flow to the epididymis, indicative of infection. (b) Abscess has caused the epididymis to take on a dilated, cystic appearance as it is displaced. On Doppler, the most vascular structure is the abscess itself.

Orchitis is inflammation of the testis. It is possible that the same *E. coli* in old asexual men and the gonorrhea and chlamydia of young sexually active men could continue their routes through the epididymis and cause bacterial infection, and therefore inflammation, of the testis. The work-up and management would be the same except with a slightly different physical exam finding (uniform scrotal swelling instead of focal superior and posterior to testes). The patient will have scrotal pain and a tender testis. It is diffuse without a specific region hurting more. There is a **positive Prehn's sign** and a **positive cremasteric reflex**. Ultrasound can be performed to rule out torsion, but is often unnecessary. However, we want you to associate orchitis not with bacterial infection but with two broad categories: adolescents who **contract the mumps virus** (parotids and testis, unvaccinated) and **autoimmune orchitis following vasectomy** (granulomatous inflammation in response to foreign bodies). Both have a similar presentation (positive Prehn's sign, positive cremasteric reflex), but there are different sequelae or histological findings. In the case of mumps, the patient must be unvaccinated and at least 10 years old to be at risk for orchitis. It is untreatable once contracted, and a variable amount of tissue may fibrose. The problem isn't the acute orchitis but rather the testicular fibrosis, subsequent lack of testosterone needed to complete puberty normally, and infertility due to low testosterone. Prevent this through vaccination. In the case of autoimmune orchitis, it is almost always because the immune system is exposed to the haploid gametes. This happens in vasectomy and trauma. On biopsy, there will be granulomatous inflammation. At first, the testis is invaded by neutrophils then macrophages (like in acute inflammation). Over time, lymphocytes arrive and induce the macrophages to become overactivated and fuse, forming the hallmark of granulomatous inflammation anywhere—**multinucleated giant cells**—in response to foreign objects (like sutures or, in this case, the haploid gametes).

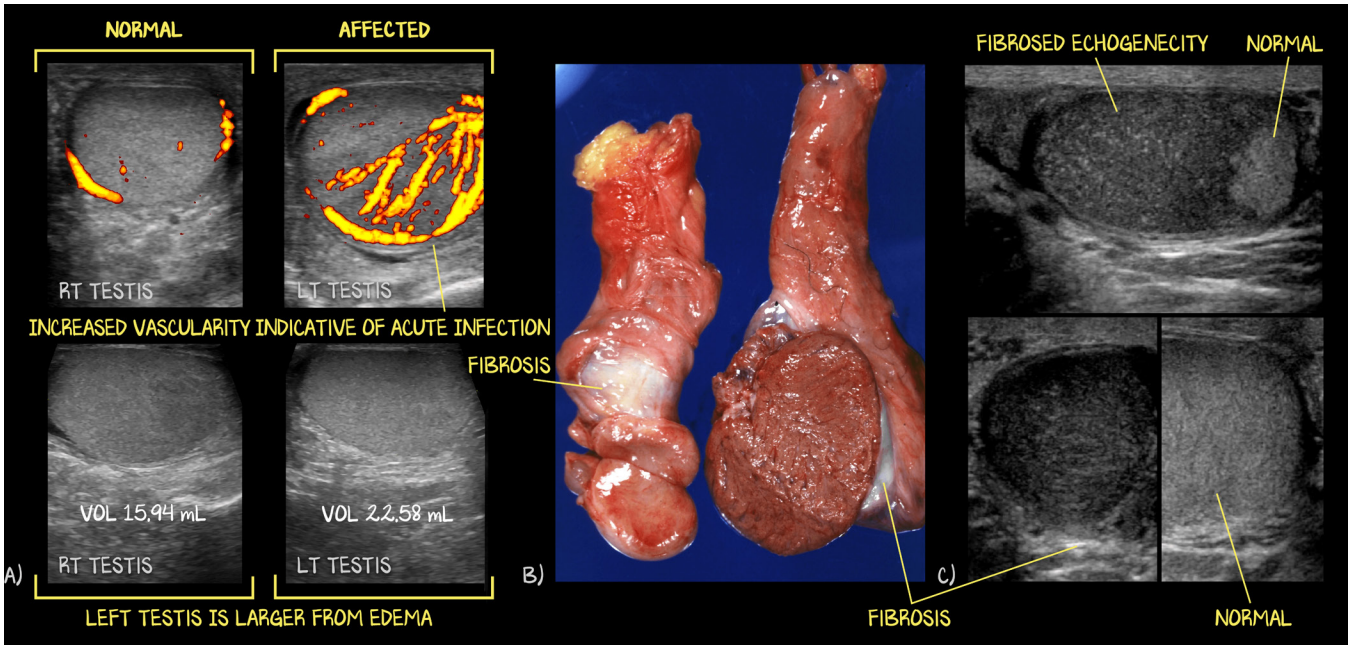

Figure 3.5: Acute Orchitis and Chronic Fibrosis of the Testis
(a) Sonograph showing increased vascularity (top row) and larger size (volume calculation reported in the bottom row) from a testis that is acutely inflamed due to the mumps virus. (b) Autopsy reveals atrophic testes and resultant white fibrosis. (c) Sonographic changes demonstrating atrophy and fibrosis. The normal tissue (light grey, without obvious fluid) is replaced by tissue with darker echogenicity, a sign of atrophy and fibrosis. The top image shows how little sparing there was of this patient's testis, most of the testis replaced by scar.

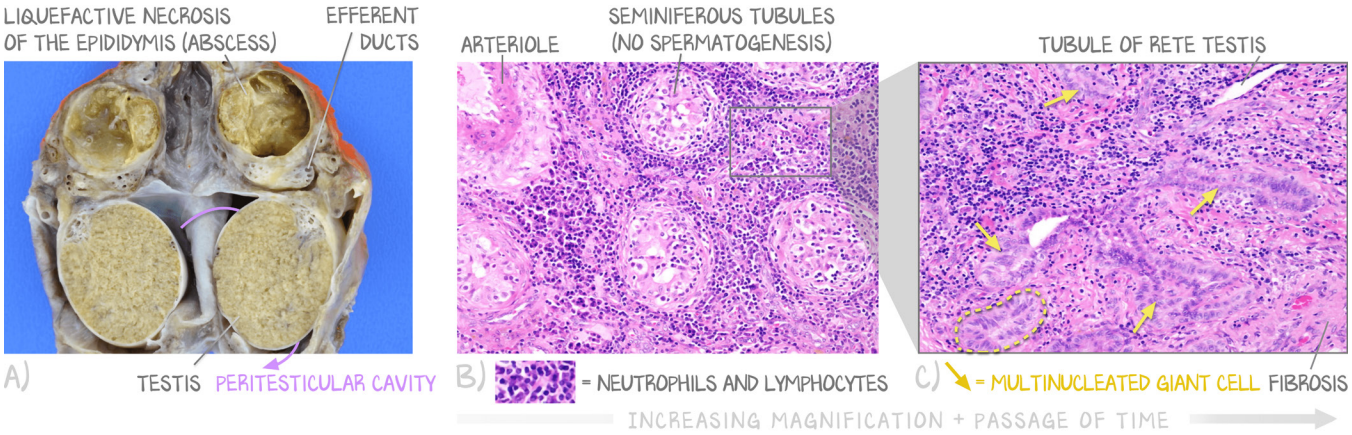

Figure 3.6: Epididymo-Orchitis
(a) An acute form of epididymo-orchitis that primarily affects the epididymis. There is a complete loss of the architecture with soup (left) and a cavity (right) instead of convoluted tubules. This was a case of a bacterial abscess. (b) Acute inflammation after vasectomy, presenting with testicular pain. There are neutrophils and lymphocytes outside the seminiferous tubules, which are small and demonstrate no spermatogenesis. (c) Taken from a different patient, this represents the natural progression of the chronic inflammatory response to spermatozoa. Multinucleated giant cells (MNGC) and lymphocytes driving the MNGC formation can be seen with barely any lumen (the white spaces) of the rete testis found. There is also evidence of fibrosis (pink stuff) on the right.

Testicular torsion is when the testis spins around within the scrotal sac. The testis is not supposed to be able to move. The gubernaculum is a fibrous band that secures the testis to the scrotal wall. And although the Peritesticular Cavity (tunica vaginalis, Body Cavity) is supposed to provide lubrication and support for the testis and the head of the epididymis, it is not supposed to encompass them. When the testis descends into the scrotal sac, it is possible that excess Peritesticular Cavity prevents the tethering

of the testis to the scrotal sac, enabling the testis to spin without anything connecting it to the scrotal wall. This has gotten the name **bell-clapper deformity**. When a large bell rings, the outer dome swings independently of the clapper within. The clapper collides with the dome of the bell to make the sound. The testis is supposed to be the bell clapper, the Peritesticular Cavity the dome of the bell. Stupid analogy (but every text includes it), as the testis does not bang against the "inside" of the Peritesticular Cavity (that's where fluid is), nor does it "bang" against anything at all—it spins. This is bad because the testis is attached to a bunch of cables within the spermatic cord—arteries, veins, and lymphatics. If the testis twists too far, it creates a knot, a **kink in the vasculature**. Which vessels are most likely to collapse? Although you may hear that what collapses first are "the thin-walled veins," heed our warning. It is indeed a venous drainage problem, but the collapse has nothing to do with being thin-walled. Arteries conduct perfusion pressure, arterioles rank down the perfusion pressure to whatever their capillaries tell them to drop it down to, and the hydrostatic pressure is exhausted across the capillary. The veins have no perfusion pressure. That also means they have no pressure pushing out from within the lumen to keep them patent. The arteries do, carrying the MAP from the left ventricle. When the vessels within the spermatic cord twist, it kinks off the low-pressure veins, and the high-pressure arteries stay open. More blood in, no blood out, and eventually, the hydrostatic pressure gets so high in the testicle that it even stops blood from flowing in. Whether due to blocked arteries or prevented arterial flow because of blocked veins, no new blood means infarction, and infarction hurts. Torsion presents with a **sudden**, **acute**, and **extremely painful** testicle. Commonly seen in **younger males** who suffer **no trauma**, especially in those with a history of **uncorrected cryptorchidism**. Uncorrected cryptorchidism means an undescended testis that has not been surgically brought down into the scrotum and sutured in place ("tacked down"). Because it is undescended, there is no connection between the scrotal wall and the testis. It must also be an uncorrected condition, as a known condition would have been surgically corrected by affixing the undescended testis to the wall of the scrotum, preventing future torsion, a surgery that is performed at age 6 months. The diagnosis is confirmed with **ultrasound with Doppler** (which can be done at the bedside). A swirling pattern on ultrasound and **no color on Doppler** (neither venous flow out nor arterial flow in) make the diagnosis. This is a **urological emergency** and must be untwisted within six hours of onset. The longer the wait, the higher the risk of loss. **Orchiectomy** is required for a testis that doesn't pink up after being untwisted, doesn't recover once its vascular supply is restored. **Orchiopexy** (surgically affixing the testis to the scrotal wall, aka "tacking it down") is performed on both the affected and unaffected testis because it is likely that whatever pathology predisposed this patient to torsion on one side is also present on the other side.

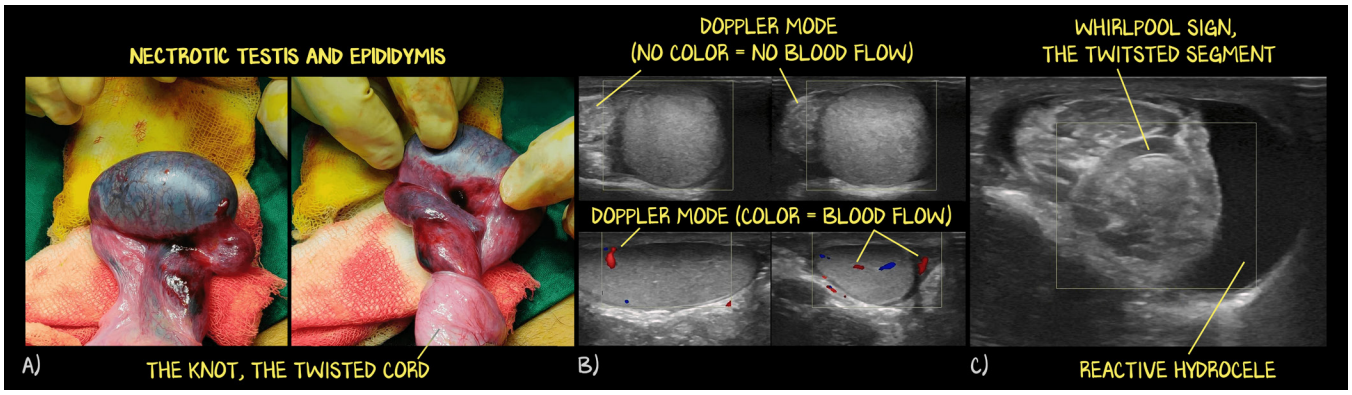

Figure 3.7: Testicular Torsion
(a) A black, necrotic testis and epididymis are shown in the photograph on the left, indicative of hemorrhagic necrosis. The testis is engorged because blood could not leave through the twisted cord. In the photograph on the right, you can see how the cord twisted about itself, choking off the venous drainage, as well as how pink the cord is proximal to the kink and how hemorrhagic (red and black) it is distal. (b) Doppler ultrasound from the same patient showing an enlarged testis without any blood flow (absence of color, large size, top two images) when compared to the normal testis below. There is evidence of a whirlpool sign and identification of a reactive hydrocele in the final image.

Testicular Cancer

Testicular cancer has many subtypes – sex cord stromal tumors, germ cell (and its many subtypes), and metastatic lymphoma. Ovarian cancer has as many subtypes, plus others. As the gynecologic oncology adage goes, "what can happen in the testis can happen in the ovary." It is for that reason we are not going into detail here in male reproduction pathologies. We will in Female Reproduction #7: *Ovarian Cancers*.

Germ cell tumors are what we're going to focus on. Even with that "shortcut," this subject gets unwieldy quickly. Focus on this: **germ cell tumors** account for 95% of testicular tumors, and of those, over half (**55%**) are **seminomas**. The other 45% are "the other ones." And when we say "ones" as a plural, we aren't being flippant or careless with our words—each individual tumor is, most of the time, not just of one type but a combination of types. When a tumor is purely of one subtype, it gets the name that it is (embryonal, yolk sac, choriocarcinoma, teratoma). But most of the time, it is a combination of tumor types, which mixes the naming. And although someone once wrote out a nice little table of tumor markers next to each tumor, the fact is that there is so much variation and integration of the cancer types that it is folly to try to explain them as discrete entities (don't worry, there is a table for you to memorize for licensure exams). We want you to focus on this:

Testicular cancer is seminoma; it is uncommon and **exquisitely sensitive to chemotherapy and radiation**.

Anything else involving cancer and the testis is not seminoma, not exquisitely sensitive to chemotherapy, and super rare (even rarer than seminoma). If you have the mental bandwidth to continue, we're going to chronicle the history of seminoma, then build you a table you can (but shouldn't) memorize of the tumors you won't see in practice because they are usually mixed (though you may see them on a licensing exam).

When there is a cancer, it is indicative of dedifferentiation. The primordial germ cells—the indifferent cells that could be induced to become spermatogonia or oogonia—migrate from the yolk sac and induce the mesothelial-derived cells to become Sertoli cells. In their differentiated form, they are cells within the basal compartment of the seminiferous tubules, acting as the stem cell niche for sperm production. They divide irregularly, so they have few opportunities to acquire mutations. Those that replicate regularly (the type B spermatogonia that turn into spermatocytes) will undergo senescence. But if one of those type A progenitors acquires enough mutations, it can lead to malignant transformation.

Seminomas are the most common type of germ cell tumor, making up about 55% of these tumors. Seminonas' peak incidence is the **third decade of life** (the full range being from about age 14 to 40), and they almost never occur in infants. An identical tumor arises in the ovary, called dysgerminoma. Seminomas **grow slowly, spread late**, and spread through **lymph nodes**. Cure rates are high. We've made a big deal about cancer genetics and comprehending cancer phenotype based on the mutation acquired (think lung cancers or colon cancers). *KIT* (something you haven't seen before in the OnlineMedEd curriculum), isochromosome 12p, and expression of NANOG and OCT3/4 (also things you haven't seen before in our curriculum) are involved in seminomas somehow (they are also involved in dysgerminoma). These are not irrelevant tumors, but their genetics are so unlike other cancer genetic pathways that they just don't fit into the framework of modular health and disease. The reason why? Ten thousand men develop testicular cancer each year. With a 95% **cure rate** (not remission, cure), 500 of those 10,000 will eventually die of testicular cancer. That's only a 5% mortality rate. We don't know much about the mechanism of testicular cancer because there are so few examples that medical science hasn't been able to map the genetics as well as it has for other, more common, more fatal conditions.

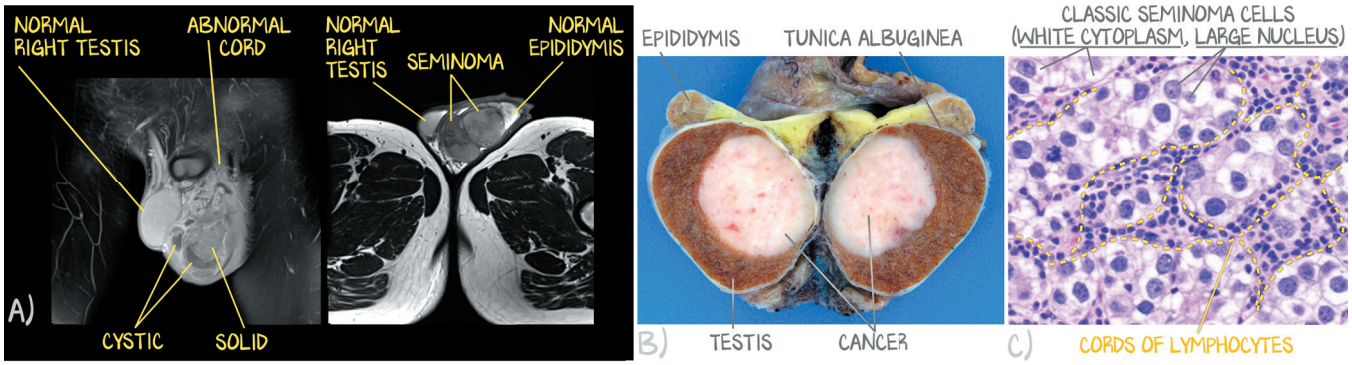

Figure 3.8: Seminoma
(a) Coronal and axial MRI demonstrating a normal-appearing right testis (left side of image) compared to the very cancerous-looking left testis (right side of image). The normal testis appears smooth and of one echogenic color (uniformly light grey, almost white). The cancerous testis is much larger, is not smooth or uniform, and displays multiple echogenicities. Compare the labeled normal right testis to the left testis, noting the multiple shades of grey, labeled solid, cystic, and seminoma. The fact that there are so many shades of grey (including the unlabeled regions) indicates something bad. (b) A different patient had a seminoma occupying the testicular medulla. There is a demarcation from clearly normal testis to clearly cancerous, but with a blurred margin. (c) The classic histological appearance consists of a uniform population of tumor cells with ample clear cytoplasm due to glycogen content and a large nucleus with a prominent nucleolus. The tumor cells are arranged in small nests or clusters separated by the trabeculae with invading lymphocytes.

Cancer usually does **not hurt**, will **not transilluminate**, and can be evaluated by **ultrasound** but ultimately requires **orchiectomy** (not needle biopsy, avoided to prevent seeding of the scrotum with cancer). Just as with all cancers, **serum markers are not used for diagnosis**, only for tracking response to therapy and relapse. **Seminomas** have the best cure rates. Anything else ("**nonseminomas**") has very poor cure rates and is usually of a mixed phenotype (expressing multiple nonseminomas in one tumor) rather than only one kind. Nevertheless, we are going to teach you discrete, individual nonseminomas because that is how they are tested on licensing exams. We're going to spend more time on the female versions of these cancers when we get there (Female Reproduction #7: *Ovarian Cancers*). This section is merely obligatory, which is why we deliver it in tabular format.

CANCER	CLASSIC FINDINGS ON LICENSING EXAMS	LAB TEST TO ASSOCIATE
Seminoma	The spermatogonia fill the seminiferous tubules, obliterate the lumen; nests of cells separated by cords of lymphocytes	Homogeneous on gross, no marker "Fried egg"
Endodermal sinus aka yolk sac	Schiller-Duval bodies, central capillary with palisading cells around it	AFP
Choriocarcinoma	Placenta cells, syncitioblasts, and cytotrophoblasts	β-hCG
Teratoma	All three germ layers, hair and teeth, 'always' malignant in males (compared to female teratoma which is 'always' benign)	All three germ layers represented
Embryonic	Worst outcome, aggressive, and if present in any nonseminoma, its presence portends poor prognosis	Hemorrhage, necrosis, and painful

Table 3.1

Cryptorchidism

The descent of the testes is an **androgen-driven process** that starts around **week 27 of development** and completes around **week 32**. Led by the gubernaculum and accompanied by the processus vaginalis (see Gastrointestinal), the testes descend from their position within the mesonephros (near the developing kidney) along the posterior wall of the abdomen, under the peritoneum, and through the inguinal canal. When a testis does not descend into the scrotal sac, it will be identified as absent on physical exam. But an **undescended testis** may still be present, just hiding somewhere along the path it was supposed to take, giving it the name crypt (hiding) orchidism (testis). We're going to continue using "undescended testis" because, although the testis seems to be missing, it usually just failed to complete its descent.

Occurring in **1% of male births**, it is the most common scrotal pathology. There are a few facts you should know, but be careful in wielding them.

A "risk factor" for developing an undescended testis is **premature birth**. The "risk" really just depends on the stage of development at birth. The descent waits for the mesonephros to involute, releasing the testis to move, and therefore must wait until the third trimester when the developing metanephroi (the kidneys) are working. If an infant is birthed prematurely—before the 30th week—the testes will not have gotten to where they would have gotten if baby had been born at full term.

The **most common site to find an undescended testis** is in the **inguinal canal**. The descent of the testis from the urogenital ridge to the pelvic wall is NOT androgen-driven and is more a product of relative growth of the organs around it than a true descent. The formation of the inguinal canal is **androgen-driven**. Although there is no overt hormonal imbalance, the fact that so many are found in the inguinal canal and not in the abdomen or pelvis indicates there may be an underlying androgenic dysfunction that has yet to be discovered and that an undescended testis is a symptom, not a diagnosis.

This is further evidenced by the fact that the **pathologic histologic changes** found within the testis starting at 2 years of age (a product of failed spermiogenesis because the inner ring of the inguinal canal is kept at core body temperature, not the reduced temperature within the scrotum) are **also found in the descended testis** (albeit to a lesser extent). It appears the pathology is present in both testes, only accelerated by being undescended. Only **25% are bilateral** (and are usually premature-birth-induced, which is, again, not an androgen dysfunction but a maturation dysfunction), so the **vast majority are unilateral**. When identified, surgical correction—**orchiopexy**—is recommended at **6 months** of age. Medical science used to recommend waiting as long as 12 months. However, if a testis is left undescended for longer than 2 years, because the temperature in the inguinal canal is too warm for Sertoli cells and spermatogonia, there is progressive **atrophy of the seminiferous tubules**, and the testis is replaced by **fibrosis**. Leydig cells remain unaffected by the temperature, but the aberrant behavior of cells **significantly increases the risk of testicular cancer** (which is why this subject is discussed where it is). The same changes happen in the unaffected testis.

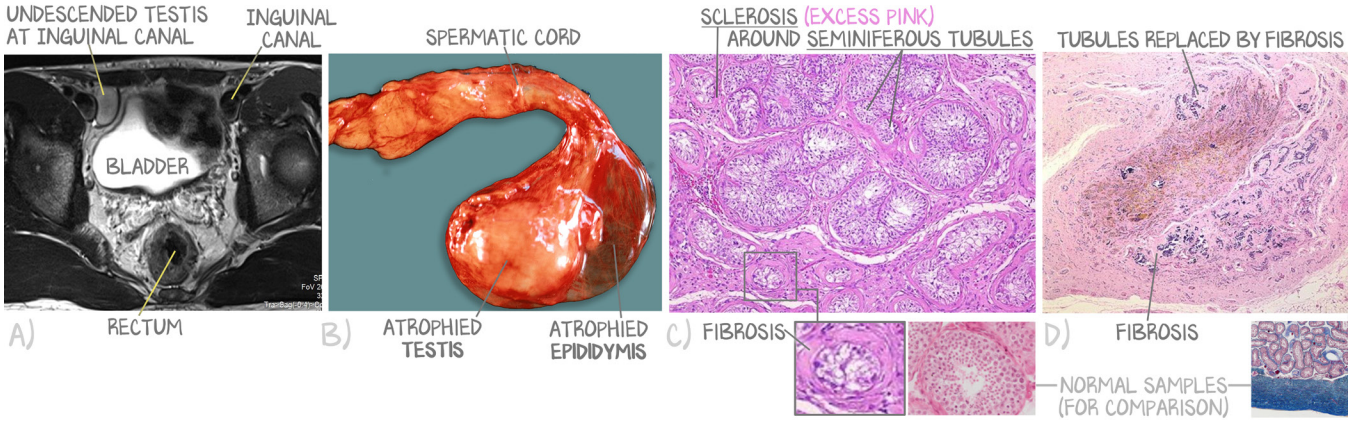

Figure 3.9: Testicular Atrophy in Cryptorchidism
(a) Axial T2-weighted MRI (fluid is bright, bone is dark) showing a pelvic testis (grey elliptical structure) where there should be none (compare to the patient's left, right side of the image). (b) Gross specimen of a testis, epididymis, and spermatic cord removed from a patient with cryptorchidism. Note the extreme atrophy. (c) The initial phase of scarring is seen in an undescended testis as early as 2 years of age. The testis demonstrates a "glassy, hyaline membrane" (pink stuff) between and encompassing the seminiferous tubules, a sign that fibrosis starts on the outside of the tubule and works its way in. There is a normal seminiferous tubule for comparison. The fibrosis is extensive and diffuse. (d) Over time, the fibrosis does indeed encroach and choke off all seminiferous tubules. The only things that remain are the pink fibrosis and white spaces lined with darkly staining blue cells (the rete testis). All seminiferous tubules are gone.

Because it has not descended, it cannot form a connection to the scrotal sac and is therefore capable of developing **testicular torsion**. With orchiopexy being performed so early, the histopathologic changes, risk of torsion, and risk of cancer have subsequently diminished.

Conclusion

That was a lot of information about the testis over three lessons. And indeed, although there has been a lot of testis, we've also telegraphed female anatomy and physiology and hinted at the rest of the male reproductive organs. In the next lesson, we discuss spermatogenesis, spermiogenesis, and the male sex act.

Citations

Figures 3.2a, 3.2b, 3.2c, 3.4, 3.5a, 3.7, 3.8a, and 3.9a: Courtesy of Radiopaedia.

Figures 3.2d, 3.5b, 3.9b, and 3.9c: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.

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